Study of the Conformation of Novel *N*-Nitrosothioureas by High-Field Nitrogen-15 and Carbon-13 Nuclear Magnetic Resonance Spectroscopy Employing Specifically Labeled Compounds

J. William Lown* and Shive M. S. Chauhan

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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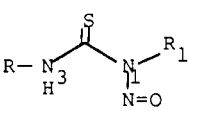
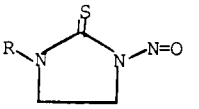
The synthesis of certain specifically $^{13}C{=}S$ and N_1, N_3, and $N{=}O$ ^{15}N-labeled novel *N*-nitrosothioureas is described. A detailed study of their high-field ^{13}C and ^{15}N NMR parameters was performed, permitting assignment of individual one-, two-, three-, and four-bond coupling constants. Low-temperature ^{13}C NMR studies in nonpolar solvents permitted the detection of several discrete conformers in the case of individual *N*-nitrosothioureas while variable temperature studies allowed a study of their equilibria. An analysis of the factors controlling the selection of preferred conformers is given as a prelude to a study of their stereoelectronically controlled decomposition under physiological conditions.

We recently described the general synthesis of the hitherto elusive *N*-nitrosothioureas.[1] This new class of compounds is of interest because of their relationship to the 1-(2-chloroethyl)-3-alkyl-1-nitrosoureas (CENUs) which have widespread clinical application in the treatment of a range of human malignancies.[2-5]

Nucleophilic addition to the amide carbon of CENUs under physiological conditions appears to be the initiating event leading to the release of electrophiles which attack cellular macromolecules[7,8] and which may therefore be ultimately responsible for the expression of anticancer properties. It follows that changing the amide group to a thioamide group in CENUs may change a number of factors including bond order, conformation, atomic size, and steric hindrance effects which control reactivity.

We report the application of high-field ^{15}N and ^{13}C NMR to the study of the structural and conformational characteristics of *N*-nitrosothioureas. This necessitated the synthesis of certain specifically ^{15}N- and ^{13}C-labeled compounds. The latter conformational properties are pertinent to attempts to correlate their stereoelectronically controlled aqueous generation of electrophiles[6] with their biological properties.





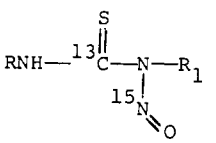
1	$R = R_1 = CH_3$	**12**, R = H
2	$R = R_1 = CH_2CH_3$	**13**, $R = CH_2CH_2OH$
3	$R = R_1 = CH_2CH_2CH_3$	
4	$R = R_1 = CH_2CH_2OCH_3$	
5	$R = R_1 = CH_2CH_2F$	
6	$R = C_6H_{11}$, $R_1 = CH_3$	
7	$R = C_6H_{11}$, $R_1 = CH_2CH_3$	
8	$R = C_6H_{11}$, $R_1 = CH_2CH_2CH_3$	
9	$R = C_6H_{11}$, $R_1 = CH_2CH_2OCH_3$	
10	$R = C_6H_{11}$, $R_1 = CH_2CH_2F$	
11	$R = C_6H_{11}$, $R_1 = CH_2CH_2OH$	

Synthesis of Specifically Labeled *N*-Nitrosothioureas

N-Nitrosothioureas **1**–**11** may be prepared by nitrosation of the corresponding thiourea under carefully controlled low-acidity (0.07–0.1 N HCl) conditions in yields of 60–90%.[1,9] The required specifically ^{15}N-labeled symmetrical thioureas **12** and **13** were prepared by reaction of carbon disulfide with (95%) ^{15}N-enriched labeled primary amines which are available commercially. ^{15}N-labeled unsymmetrical thioureas **16** were prepared by reaction of an alkyl isothiocyanate with an ^{15}N labeled primary amine.

The thioureas were examined by ^{15}N NMR, ^1H NMR and mass spectrometry to confirm the position and extent of substitution. When the additional nitroso ^{15}N-labeled *N*-nitrosothioureas **2a**, **3a**, and **7a** were required this was accomplished by treating the corresponding thioureas with $Na^{15}NO_2$ in 0.07 N HCl.[1,9] The ^{15}N-labeled imidazolidinethione **16** required for conformational studies and assignment of ^{15}N coupling constants was prepared by the reaction of ^{15}N-labeled ethylenediamine with carbon disulfide and nitrosated to give **12a** as shown in Scheme I.

The specifically $^{13}C{=}S$-labeled *N*-nitrosothioureas **17**–**20**



18	$R = R_1 = CH_3$
19	$R = R_1 = CH_2CH_3$
20	$R = R_1 = CH_2CH_2CH_3$
21	$R = C_6H_{11}$, $R_1 = CH_2CH_3$

were prepared by reaction of the appropriate amine with

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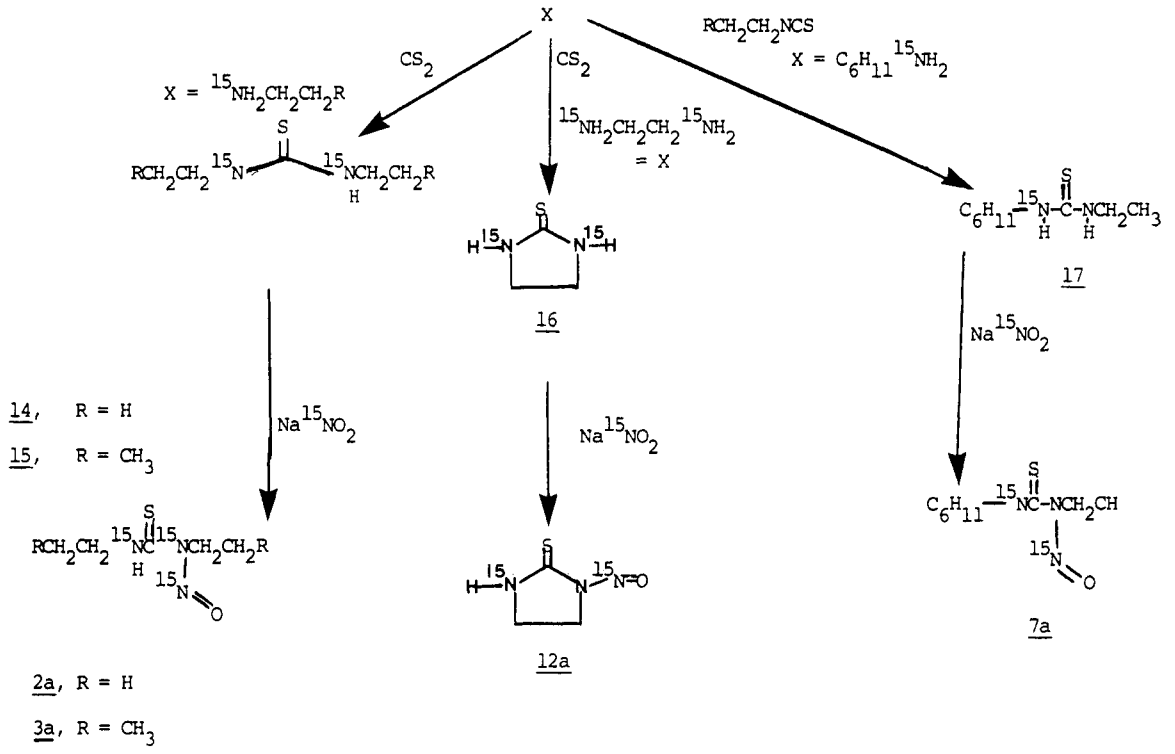
Scheme I



labeled phosgene (90% ^{13}C enrichment) as described previously.[1] The ^{15}N-labeled nitroso group was then introduced as before employing the low acidity 0.07 N HCl procedure. The extents of the incorporation of ^{13}C and ^{15}N were confirmed by ^{13}C NMR, ^{15}N NMR and mass spectra.

Nuclear Magnetic Resonance Spectra of *N*-Nitrosothioureas

The ^1H NMR spectral characteristics of *N*-nitrosothioureas have been reported.

^{15}N NMR Spectra. The high sensitivity of ^{15}N NMR to molecular interaction, hydrogen bonding, and dynamic changes in solution as well as the possibility of detecting the diazohydroxide, during their decomposition under physiological conditions prompted us to examine the ^{15}N spectra of nitrosothioureas.

Chemical Shifts. There have been few reports concerning the ^{15}N shifts in thioureas. However, it is known that they depend strongly on the nature of attached alkyl groups, i.e., δ 73.5, 110.5, 112.3 and 128.0 for the methyl, ethyl, *n*-propyl, and cyclohexyl symmetrical thioureas in acetone.[10] Upon N_1-nitrosation of thioureas, the corresponding N_3 nitrogens of *N*-nitrosothioureas appear at δ 98.5, 134.2, 132.2, and 142.3 in the same solvent (acetone). The ^{15}N chemical shifts of the N_1 nitrogens of the *N*-nitrosothioureas appear in the range of δ 273.6–285.3 and show a strong substituent dependence (see Table I). These differences in chemical shifts may be due to changes in the sp^3 character of the nitrogen lone pair and to its delocalization.

The ^{15}N chemical shift of the $^{15}N{=}O$ resonates slightly upfield at δ 552.2–560.9 relative to the N=O group in nitrosoureas[6] (δ 559.9–569.3) in the same solvent, indicative of less electron delocalization in the former case. The $^{15}N{=}O$ chemical shifts also move downfield upon increasing the solvent polarity and basicity which may be attributed to solvent interaction with the nitrogen lone pair in N–N bond rotation (vide infra).

Table I. ^{15}N Chemical Shifts of *N*-Nitrosothioureas[a]

	solvent (concn, M)	chemical shift, δ		
		NH	>N	N=O
1	$CHCl_3$ (1)	98.5	273.7	556.0
2a	acetone (0.01)	134.2	286.2	560.3
2	$CHCl_3$ (1)	130.5	285.3	556.1
2a	$CHCl_3$ (0.01)	129.6	285.0	556.1
3a	$CHCl_3$ (0.01)	126.5	284.6	555.3
3a	acetone (0.01)	132.2	285.3	561.7
3a	Me_2SO (0.01)	141.4	286.0	561.4
3a	CF_3CH_2OH (0.01)	131.4	284.0	556.4
4a	$CHCl_3$ (0.01)	*b*	*b*	558.8
5	$CHCl_3$ (1)	118.0	276.6	559.6
6	$CHCl_3$ (1)	141.9	273.6	555.5
7	$CHCl_3$ (1)	141.1	285.2	552.2
9	$CHCl_3$ (0.01)	142.2	*b*	556.9
10	$CHCl_3$ (1)	142.6	275.8	557.5
11	$CHCl_3$ (1)	143.9	279.5	557.7
7a	acetone (0.01)	145.8	*b*	560.3

[a] Proton-decoupled spectra were recorded by using dimethylformamide as an external standard, and values were reported with NH_3 as 0.0 ppm; 80 000–85 000 scans were required for the natural-abundance spectra with 0.05 M tris(acetylacetone)chromium as a relaxing agent. Approximately 500–100 scans are required for ^{15}N-enriched compounds. [b] Unenriched nitrogens were not observed for the concentration and number of scans used.

^{15}N–^1H Coupling. The one-bond coupling constants in nitrosothioureas show values of 89.2–89.6 Hz in chloroform and increase to 92.7 Hz in more polar solvents, e.g., acetone. In the case of the cyclic nitrosothiourea **15** in acetone the $^1J(^{15}N{-}^1H)$ is 100.0 Hz. A similar high value of the one-bond coupling has been observed in the case of cyclic ureas[11] and peptides as well as thiohydrazides where the N–H proton may be out of the plane of the C=S bond.[12,13]

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The values of $^1J(^{15}N-^1H)$ observed for the nitrosothioureas in $(CD_3)_2SO$ of 91.2 Hz is close to the reported trans coupling constant in the case of peptide bond.[6,13]

There is no detectable $^3H^{15}N-^1H$ interaction between the $^{15}N{=}O$ and protons α to the N_1 nitrogen in either nonpolar ($CDCl_3$) or polar [$(CD_3)_2SO$] solvents. This result which is in contrast to the *N*-nitrosoureas[6] may indicate that the alkyl group is syn to the N=O group or that they are not coplanar.[14,15] Four-bond couplings $^4J(^{15}N(N{=}O)-^1H)$ have been reported to be small[16] but in the N-nitrosothioureas **2a** and **3a** are in the range of 1.6–2.1 Hz, while a higher value of 4.0 Hz is obtained in the case of **15** in acetone which may well adopt a W conformation.

$^{15}N-^{15}N$ Coupling. The one-bond coupling constants for *N*-nitrosothioureas are in the range of 21.8–22.4 Hz and are greater than other reported $^1J(^{15}N-^{15}N)$ values,[6,17,18] and may be due to the electron withdrawal effect of the adjacent thiocarbonyl group (see Table II). The two bond $^2J(^{15}N-^{15}N)$ values for *N*-nitrosothioureas are 0.5–1.0 Hz in contrast to the two bond coupling in nitrosoureas of 2.0–3.0 Hz. The three-bond $^3J(^{15}N-^{15}N)$ values in nitrosothioureas are strongly solvent dependent in the range 2.5–3.9 Hz compared with values of 1.4–2.8 Hz for nitrosoureas.[6]

^{13}C NMR Spectra. A detailed study of the ^{13}C NMR of nitrosoureas was warranted since specific ^{13}C labeling of the carbonyl carbon of nitrosoureas has been informative in connection with the study of tetrahedral intermediates during their decomposition under physiological conditions.[6] The $^{13}C{=}S$ signals in thioureas appear at δ 181.21–182.75 in $CDCl_3$ (Table III) while the comparable carbons in nitrosothioureas appear at δ 179.21–181.26, which may be attributed to electron withdrawal by the nitroso group at the N_1 nitrogen. The ^{13}C chemical shifts of the α and β carbons in nitrosamines[19] and nitroso-*N*-alkyl amino acids[20,21] have been taken as characteristic of syn and anti orientations with respect to the nitroso group. The ^{13}C resonances on the alkyl groups adjacent to the N_1 nitrogen by analogy thereby indicate that they are syn to the nitroso group provided they are coplanar (Table III). The $^{13}C{=}S$ resonances of **10** at −78 °C in acetone appear as two distinct signals at δ 177.98 and 180.12 which are ascribed to the two individual conformers (see below). Similar chemical shift differences of carbonyl carbons have been attributed to the existence of *E* and *Z* isomers in the case of hydrazides and related structures.[22-24]

$^{15}N-^{13}C$ Coupling. The observed one-bond couplings $^1J(^{15}N_3-^{13}C_{C=O})$ in nitrosothioureas are 16.2–18.2 Hz (Table II), i.e., somewhat lower than those for their oxygen counterparts which are in the range 21.5–24.5 Hz. Similarly the $^1J(^{15}N_1-^{13}C_{C=O})$ values in nitrosothioureas appear in the range 12.5–13.6 Hz, substantially smaller than for

Table II. ^{15}N Coupling Constants for *N*-Nitrosothioureas

compd	solvents	proton coupling,[a] Hz($^1J^{15}N_3$-H)	^{13}C coupling constants,[b] Hz				^{15}N coupling constants,[c] Hz	
			$^1J(^{13}C-^{15}N_3)$	$^1J(^{13}C-N_1)$	$^2J(^{13}C_{C=O}-{}^{15}N_{N=O})$	$^1J(^{13}C-^{15}N_1)$	$^1J(^{15}N-^{15}N)$	$^3J(^{15}N-^{15}N)$
3a	$CHCl_3$	89.2	18.2 ± 0.2	12.5 ± 0.2	3.6 ± 0.2	8.0	22.2 ± 1.5	3.8 ± 1.5
3a	acetone	92.7	17.5 ± 0.2	12.7 ± 0.2	3.7 ± 0.2	8.1	22.4 ± 0.2	3.2 ± 0.2
2a	$CHCl_3$		16.2 ± 0.2	13.6 ± 0.2	3.2 ± 0.2	7.8	22.2 ± 1.5	2.7 ± 1.5
2a	acetone						22.2 ± 1.5	2.2 ± 1.5
3a	Me_2SO	91.2	17.0 ± 0.2	13.0 ± 0.2	4.0 ± 0.2		22.3 ± 0.2	2.5 ± 0.2
3a	CF_3CH_2OH	91.0					21.8 ± 0.2	3.5 ± 0.2
12a	acetone	100.0					21.1 ± 0.2	3.9 ± 1.0
7a	acetone	91.0[d]	18.4 ± 0.2		4.1 ± 0.2	10.5 ± 0.2		

[a] $^4J(^{15}N_3-H)$ coupling constant are 1.6–1.8 Hz in acyclic nitrosothioureas **2a**, **3a**, and **7a**, whereas $^4J(^{15}N_3-H)$ for **15** is 4.0 Hz. [b] $^3J(^{13}C_1-{}^{15}N_{N=O})$ are less than 1.8 Hz for nitrosothioureas **2a** and **3a**, whereas this coupling constant for **15** is 2.4 Hz. [c] $^2J(^{15}N-{}^{15}N)$ for acyclic nitrosothioureas **2a** and **3a** are 0.5–1.0 Hz. [d] $^1J(^{15}N-H)$ in $CDCl_3$ is 90.0 Hz.

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Table III. ^{13}C Chemical Shifts of *N*-Nitrosothioureas

SN	solvents	chemical shift, δ (coupling const, Hz)							
		C=S	C_1	C_2	C_1'	$C_2'C_6'$	$C_3'C_5'$	C_4'	C_3
1	$CDCl_3$	181.26	30.72		32.93				
2	$CDCl_3$	179.21	38.69	12.03	41.31	13.49			
2	acetone-d_6 [a]	180.50	38.99	12.28	42.00	13.48			
2	acetone-d_6 [b]	179.50	39.30	10.30	41.34	13.23			
3	$CDCl_3$	180.10	44.73	20.37	47.95	20.66	11.49		11.25
3	acetone-d_6 [a]	180.92	45.12	20.90	48.34	21.84	11.60		11.34
3a	acetone-d_6 [c]	180.16	45.08	20.94	48.42	21.88	11.78		11.33
3	acetone-d_6 [b]	179.85	45.12	20.65	48.00	21.64	11.78		11.48
4	$CDCl_3$	180.34	41.88	68.42	44.97	69.42	58.92		58.81
5	$CDCl_3$	180.59	42.24 ($^2J_{^{13}C\text{-}F}$ = 23.8)	78.8 ($^1J_{^{13}C\text{-}F}$ = 171.8)	48.43 ($^2J_{^{13}C\text{-}F}$ = 20.0)	81.24 ($^1J_{^{13}C\text{-}F}$ = 168.7)			
6	$CDCl_3$	178.81	30.50		54.80	31.88	24.71	25.50	
7	$CDCl_3$	178.21	38.64	12.05	54.70	31.89	24.71	25.50	
8	$CDCl_3$	178.62	44.68	20.23	54.66	31.88	24.71	25.07	
9	$CDCl_3$	178.62	41.80	68.63	54.82	31.87	24.68	25.54	58.82
10	$CDCl_3$	178.20	40.00 ($^2J_{^{13}C\text{-}F}$ = 20.0)	79.82 ($^1J_{^{13}C\text{-}F}$ = 172.6)	54.90	31.84	24.76	24.49	
11	$CDCl_3$	179.37	45.10	59.95	53.08	31.78	24.66	25.44	

[a] All the spectra in $CDCl_3$ and acetone-d_6 were recorded at 31 °C. [b] The spectra was recorded at −80 °C. [c] The higher field position of thiocarbonyl carbon in acetone may be due to a nitrogen-15 isotope shift in this case.

the comparable values in nitrosoureas of 16.2–18.3 Hz. Carbon coupling constants depend on a number of factors including the Fermi contact term, hybridization, and bond order as well as solvent polarity.[16,25,26] When compared in the same solvents, the $^1J(^{15}N\text{–}^{13}C)$ values of both types for nitrosothioureas are significantly smaller which may reflect the lower electronegativity of the sulfur and the consequent lower delocalization and the lesser double bond character of the C–N bonds adjacent to sulfur and/or increased S character of the C=S carbon compared with nitrosoureas.

The two-bond $^2J(^{15}N_{N=O}\text{–}^{13}C_{C=O})$ values in nitrosothioureas are 3.2–4.0 Hz and are somewhat smaller than those for their oxygen counterparts of 3.7–5.1 Hz where, in the average conformation, the nitroso group is anti to the carbonyl group. The $^2J(^{15}N_{N=O}\text{–}^{13}C_1)$ coupling between nitrogen and the adjacent sp^3-hybridized α carbon at ambient temperatures is <1.8 Hz which is indicative of a syn relationship between these atoms.[6,27] The observed decrease in the value of this type of coupling in the case of **10a** from 3.7 Hz at 263 K to 1.8 Hz at 300 K is attributed to an averaging of the coupling owing to $C\text{–}N_1$ bond rotation and nitrogen pyramidal inversion.[6]

Conformational Preference in *N*-Nitrosothioureas in Solution

At room temperature the natural-abundance ^{13}C carbonyl signals in *N*-nitrosothioureas are broad and of low intensity in the region of δ 178.21–181.26 which may be attributed to an unusually long relaxation time. At lower temperatures (−80 °C) the signals sharpen and increase in intensity without any significant changes in chemical shifts (see Figures 1 and 2). Specific enrichment of the thiocarbonyl carbon with ^{13}C and of the nitroso group nitrogen with ^{15}N and an examination of the ^{13}C spectrum at different temperatures is informative since several different conformers (see Figure 3) are revealed by their chemical shifts and characteristic $^2J(^{13}C\text{–}^{15}N)$ coupling constants. The presence of a single conformer for each nitrosothiourea (**19–21**) in nonpolar solvents such as CD_2Cl_2 and tetrahydrofuran-d_8 even at −80 °C suggests that rotation about single bonds as well as atomic inversion of nitrogen is fast on the NMR time scale in these solvents.

The sharp NH stretching and vibration band as well as the magnitude of the $^2J(^{15}N\text{–}^{13}C)$ coupling constant between the nitroso nitrogen and the thiocarbonyl carbon in **1** and **3** in CCl_4 or $CHCl_3$ solution reveals that there is possibly a weak intramolecular hydrogen bond between the N_3H and the nitroso nitrogen lone pair, but there is no evidence of a strong intramolecular hydrogen bond. Although discrimination between hydrogen bonding with the nitroso group oxygen and the nitroso group nitrogen lone pair in nonpolar solvents is difficult at present, the high value of $^2J(^{15}N\text{–}^{13}C_{C=O})$ = 3.8 Hz favors lone pair intramolecular hydrogen bonding under these conditions. A similar type of intramolecular hydrogen bonding with the unshared electron pair has been reported.[28,29] The variation of the values of the NH and NO ^{15}N chemical shifts from $CHCl_3$ to $(CD_3)_2SO$ for **3a** (Table I) appear to indicate that polar solvents may interact with the NH proton and the nonbonded electron pairs of the electronegative atoms in the molecules.[29]

The presence of two major conformers of *N*-nitrosothiourea **18** in a ratio of 1:4 is detected at −80 °C in acetone-d_6 at δ 180.79 [$^2J(^{15}N\text{–}^{13}C)$ = 3.8 Hz; Figure 2]. This indicates the importance of solvent effects which retard either the rate of rotation or of atomic inversion at this temperature by interacting with the NH proton or the lone pair of the nitroso group nitrogen. Similar results were obtained with **18** by using ethanol-d_6 in which two conformers were detected at δ 180.43 [$^2J(^{15}N\text{–}^{13}C)$ = 3.7 Hz] and 180.41 [$^2J(^{15}N\text{–}^{13}C)$ = 3.7 Hz] which may not be attributed to the isotope shift due to the complete exchange from NH to ND under these conditions.[30] The two signals persisted at the same positions in the same ratio as was observed in acetone when solvent mixtures of acetone-d_6

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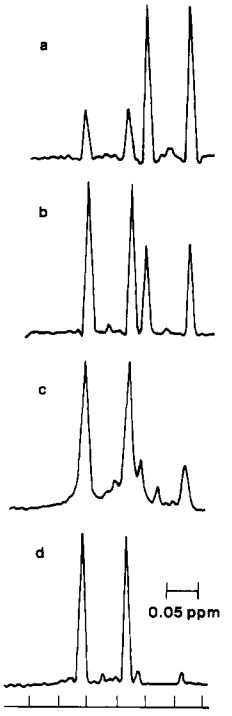


Figure 1. Proton-decoupled resolution-enhanced ^{13}C NMR spectra (Bruker WH200 instrument operating at 50.32 MHz) of ^{13}C=S-enriched **18–21** (a–d, respectively) in $(CD_3)_2CO$ at −80 °C, employing 16K data points with a pulse width of 30 μs, a pulse angle of 36°, and a repetition rate of 8.192 s. Gaussian multiplication was applied to FID for resolution enhancement by employing parameters GB = 0.2 and LB = 0.7.

and dichloromethane-d_2 were used. The decrease in intensity of the δ 180.41 resonance suggests that this peak is due to a conformer which is subject to solvent interaction. Similar results were obtained by using ^{13}C-enriched nitrosothiourea **19** which showed different conformers at −80 °C in acetone-d_6 and ethanol-d_6 but a single conformer in CD_2Cl_2 or THF-d_8. Similarly, ^{13}C-enriched *N*-nitrosothiourea **20** in acetone-d_6 at −80 °C reveals the existence of four distinct conformers: δ 180.22 [$^2J(^{15}N–^{13}C)$ = 3.8 Hz], 180.16 (^2J = 3.8 Hz), 180.12 (^2J = 3.8 Hz), and 180.10 (^2J = 3.8 Hz). The progressive effect of increasing the bulk of the N_3 substituent in the *N*-nitrosothioureas on the preferred conformations in a given solvent is evident in the case of **18–21**. It may be seen from Figure 1, which shows the ^{13}C=S signals of the specifically enriched compounds in $(CD_3)_2CO$ at −80 °C, that in each case there are two major conformers. As the steric bulk of the N_3 substituent increases from CH_3 to CH_3CH_2 to $CH_3CH_2CH_2$, to cyclohexyl, the ratio of the two preferred conformers progressively changes from 1:4 to 4:1. One contributing factor may be that as the bulk of R_3 increases the NH proton becomes less accessible to interact with the solvent.

In the case of **20** the ^{13}C peaks at δ 180.10 and 180.12 diminish as the temperature increases and are undetectable at 20 °C while the δ 180.16 and 180.22 peaks broaden and collapse at 40 °C (Figure 2). The temperature dependence signifies rotation about the single bonds and/or pyramidal inversion of the N_1 nitrogen atom or an inversion at the trigonal nitroso nitrogen atom. During pyramidal inversion the atom passes through a transition state in which the lone pair resides in a pure p orbital and in which the bonds from the central atom are sp^2 in character.[31] In *N*-nitrosothioureas the N_1 nitrogen is conjugated with two π-acceptor groups, S=C—NR and N=O, the effect of

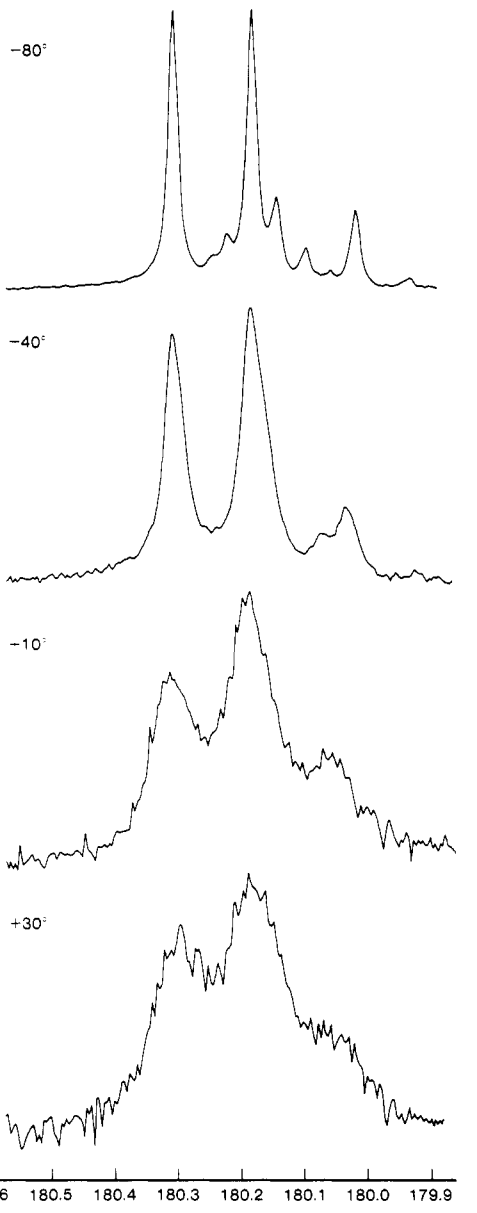
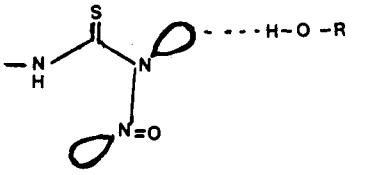


Figure 2. Proton-decoupled resolution-enhanced ^{13}C NMR signals due to 90% ^{13}C=S-enriched **20** in $(CD_3)_2CO$ revealing the existence of discrete conformers at different temperatures. The experimental conditions for the resolution-enhanced spectra were as described in the legend for Figure 1.

which is to lower the barrier to inversion below the range of detection by NMR methods. If the lone pair of the N_1



nitrogen is hydrogen bonded with the solvent, however (see below), the rate of pyramidal inversion is substantially slowed. Solvent interactions of this type have been reported by Chow[32] in the example of nitrosoamide photolysis.

In the case of unsymmetrically substituted *N*-nitrosothioureas there are eight types of possible conformations to be considered (Figure 3, a–h). Nonbonded steric interactions between the alkyl groups render conformers c,

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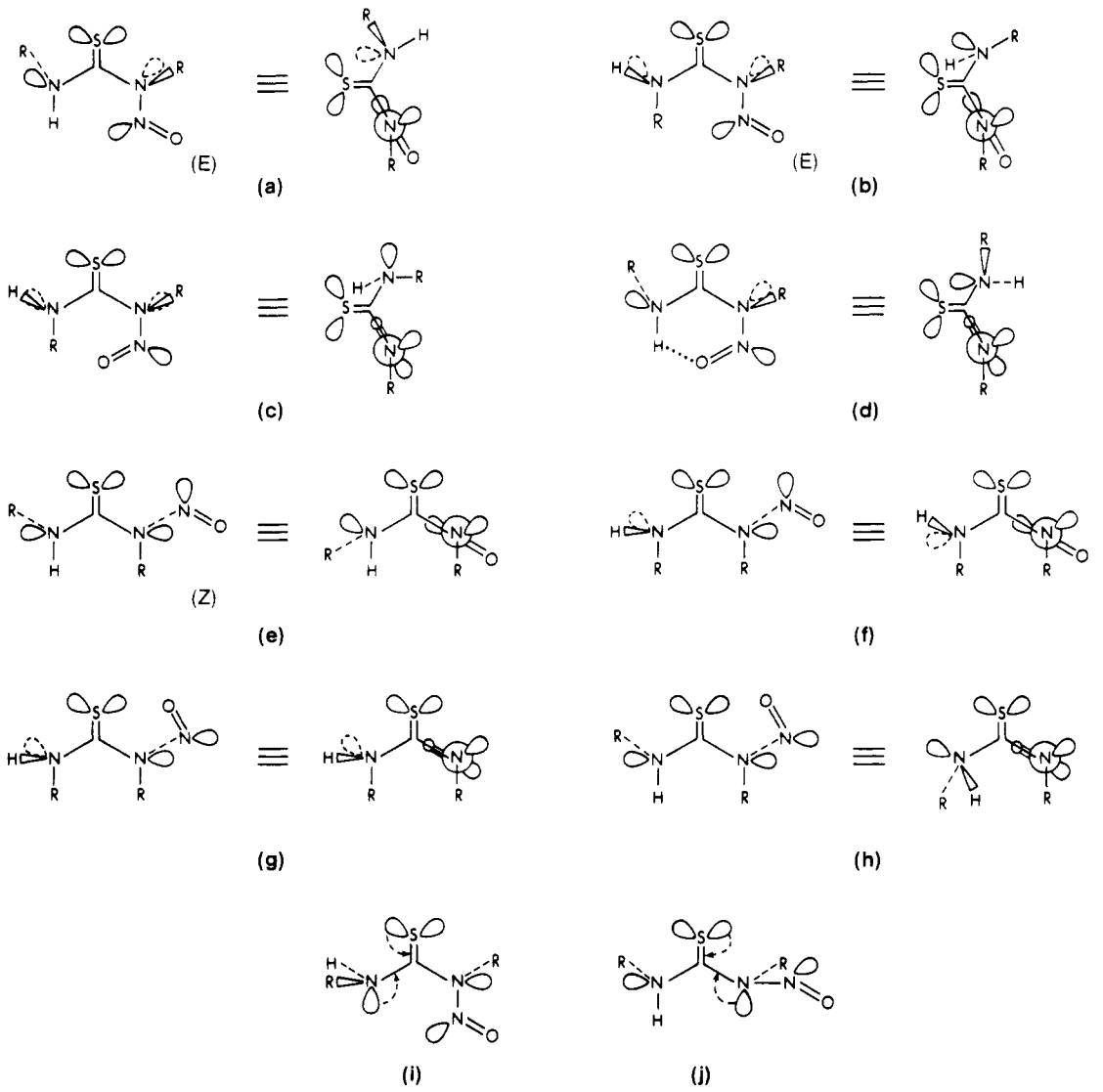

Figure 3. Alternative conformers of *N*-nitrosothioureas.

f, and g unfavorable. The π-bond repulsion between the C=S and N=O groups in conformers g and h also make these conformations unfavorable while the absence of any firm evidence for intramolecular hydrogen bonding tends to exclude conformer d. The infrared spectra of the *N*-nitrosothioureas in nonpolar solvents thus favor the remaining conformers a and e over b where the NH proton is trans to the C=S bond.

A differentiation between conformers a and e in individual cases may be made by invoking the Edward–Lemieux effect[33,34] which, in this case, predicts that the *Z* conformer, in which the N_1 lone pair orbital is antiperiplanar to the C=S bond, is more stable than the *E* conformer. In addition, antiperiplanar orbitals on pyramidal nitrogen are disfavored energetically compared with the structure which contains the maximum number of gauche interactions.[35,36] The magnitude of the dihedral angle between adjacent lone pairs may also be decisive in determining the rate of inversion at both nitrogens and the rate of rotation about The N_1–N_{NO} bond. Such factors might govern the thiocarbonyl reactivity and proton-accepting abilities of nitrogens as in the case of hydrazine[23] and hydrazines.[37] A discussion of the implications of the conformational analysis and stereoelectronic control[37] in the alternative pathways of decomposition adopted by the individual conformers of those novel *N*-nitrosothioureas under physiological conditions will appear in a subsequent publication.

Experimental Section

The IR spectra were recorded on a Nicolet 7199 FT spectrophotometer and only the principal, sharply defined peaks were reported. The ^1H NMR spectra of the intermediates were recorded on Perkin-Elmer 90 and Varian HA-100 analytical spectrometers, and those of the final nitrosoureas were recorded on Bruker WH-200 and WH-400 spectrometers. The spectra were measured on approximately 5–10% (w/v) solutions, depending upon the spectrometers, in appropriate deuterated solvents with tetramethylsilane as an internal standard. Most of the ^{13}C spectra were recorded on a Varian HA-60 and Bruker HEX-90 spectrometers, relative to tetramethylsilane. The ^{13}C spectra of specifically ^{15}N-labeled compounds were recorded on a Bruker WH-200 spectrometer.

The ^{15}N spectra were recorded on a Bruker WH-200 spectrometer operating at 20.283 MHz. The spectra were recorded by using dimethylformamide as an external reference, and

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chemical shift values are reported relative to 10–20% ammonia at 0.0 ppm with the respective deuterated solvent as a lock signal. Most of the proton-decoupled natural-abundance ^{15}N spectra were obtained by using a 1 M sample solution with 0.05–0.1 M Cr(AcAc)$_3$ in a 20-mm-diameter tube after 80–86K scans. The spectra of specifically labeled compounds were recorded with 0.01 M solutions with or without Cr(AcAc)$_3$ (0.01–0.1 M) by using approximately 1–4K scans.

Materials. The required alkylamines were obtained from Aldrich, and alkyl isothiocyanates were obtained from Trans World Chemicals. Sodium nitrite-^{15}N (95–99%), carbon-^{13}C disulfide (90%), and ethylamine-^{15}N hydrochloride (95%) were obtained from Merck Sharp and Dohme. Propylamine-^{15}N hydrochloride was prepared from potassium phthalimide-^{15}N (99%) and propyl iodide as described for 2-chloroethylamine-^{15}N hydrochloride.[6] 1,3-Diaminopropane-$^{15}N_1$,$^{15}N_3$ dihydrochloride was prepared from potassium phthalimide-^{15}N (99%) and 1,3-dibromopropane by following the literature procedure.[38] Cyclohexylamine-^{15}N was prepared from the reduction of aniline-^{15}N (99%) with hydrogen in the presence of 5% Pd on alumina by following the literature procedure.[6] The following nitrosothioureas were prepared by following the method described in the preceding paper.[1] N_1,N_3-dimethyl-N_1-nitrosothiourea (**1**), mp 46 °C; N_1,N_3-diethyl-N_1-nitrosothiourea (**2**), heavy oil; N_1,N_3-dipropyl-N_1-nitrosothiourea (**3**), heavy oil; N_1,N_3-(2-methoxyethyl)-N_1-nitrosothiourea (**4**), oil; N_1,N_3-bis(2-fluoroethyl)-N_1-nitrosothiourea (**5**), mp 23 °C; N_3-cyclohexyl-N_1-methyl-N_1-nitrosothiourea (**6**), mp 35–36 °C; N_3-cyclohexyl-N_1-ethyl-N_1-nitrosothiourea (**7**) mp 42 °C; N_3-cyclohexyl-N_1-*n*-propyl-N_1-nitrosothiourea (**8**), heavy oil; N_3-cyclohexyl-N_1-(2-methoxyethyl)-N_1-nitrosothiourea (**9**), heavy oil; N_3-cyclohexyl-N_1-(2-fluoroethyl)-N_1-nitrosothiourea (**10**), mp 51–52 °C; N_3-cyclohexyl-N_1-(2-hydroxyethyl)-N_1-nitrosothiourea (**11**), mp 55–57 °C.

3-Nitrosoimidazoline-2-thione (12) was prepared from imidazoline-2-thione [^{1}H NMR (Me$_2$SO-d_6) δ 3.50 (s, 4 H, CH$_2$), 8.00 (br m, 2 H, NH, exch); ^{13}C NMR (Me$_2$SO-d_6) δ 44.00 (C$_4$, C$_5$), 183.49 (C=S)] and NaNO$_2$/0.1 HCl by following the literature procedure:[39] ^{1}H NMR (Me$_2$SO-d_6) δ 3.45 (s, 4 H, CH$_2$), 10.40 (br m, 1 H, NH exch); ^{13}C NMR (acetone-d_6) δ 42.71 (C-5), 44.36 (C-4), 180.14 (C=S); MS, *m/e* (relative intensity) 131.0155 (100.00, M$^+$; calcd 131.0153).

1-(2′-Hydroxyethyl)-3-nitrosoimidazoline-2-thione (13). 1-(2′-Hydroxyethyl)imidazoline-2-thione was prepared according to the method of Mckay and Vavasor:[40] 85% yield; mp 135 °C (lit.[41] mp 136.5–137.5 °C); NMR Me$_2$SO-d_6) δ 5.50 (br m, 8 H, CH$_2$), 4.75 (br m, 1 H, OH, exch), 8.00 (br m, 1 H, NH, exch); ^{13}C NMR (Me$_2$SO-d_6) δ 182 (C=S), 58.85 (C$_2$′), 49.16 (C$_4$), 48.56 (C$_1$′), 40.95 (C$_3$). The above 1-(2′-hydroxyethyl)imidazoline-2-thione (2.80 g, 0.02 mol) and sodium nitrite (1.4 g, 0.02 mol) in dichloromethane were treated with dilute HCl (0.1 N, 200 mL) dropwise during 1 h. The reaction mixture was stirred for 30 min at 0 °C. The organic layer was removed, washed with water, and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure, and the residue was crystallized from ethanol to afford **13**: 2.52 g (75% yield); mp 128 °C (lit.[41] mp 127–128 °C); IR (KBr) 3415 (NH), 1530 (CNH), 1445 (N=O) 1210, 1145 (C=S) cm^{-1}; NMR (Me$_2$SO-d_6) δ 3.82 (m, 4 H, CH$_2$), 3.95 (s, 4 H, CH$_2$), 4.85 (m, 1 H, OH exch); ^{13}C NMR (Me$_2$SO-d_6) δ 42.18 (C-5), 48.15 (C$_2$′), 49.48 (C-4), 57.14 (C$_2$′), 175.98 (C=S).

3-(Nitroso-^{15}N)-imidazoline-2-thione-*1,3*-$^{15}N_2$ (12a). Imidazoline-2-thione-*1,3*-$^{15}N_2$ [**16**: NMR (acetone-d_6) δ 3.8 (m, 4 H, CH$_2$), 7.0 (d, 2 H, NH, $^{15}J_{N-H}$ = 100.0 Hz)] was prepared from CS$_2$ and 1,2-diaminoethane-*1,2*-$^{15}N_2$ hydrochloride (1.50 g, 10 mmol) with an equivalent amount of sodium hydroxide by refluxing for 12 h. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate to afford 520 mg (50%) of **16** which was nitrosated with Na^{15}NO$_2$ (360 mg, 5 mmol) in the presence of 0.7 N HCl at −5 °C. After the usual workup the 3-nitrosoimidazoline-2-thione (**12a**; 200 mg, 30% yield) was obtained as yellow crystals: ^{1}H NMR (acetone-d_6) δ 3.90 (m, 4 H, CH$_2$), 9.45 (ddd, ^{15}J(N–H) = 100.0 Hz, $^3J(^{15}NH–N_1)$ = 4.0 Hz, $^4J(^{15}NH–^{15}N=O)$ = 4.0 Hz); MS, *m/e* (relative intensity) 134.0065 (100.00; calcd for $C_3H_5{}^{15}N_3OS$, 134.0065).

1,3-Dipropyl-1-(nitroso-^{15}N)-thiourea-*1,3*-$^{15}N_2$ (3a). To a solution of CS$_2$ (0.5 g, 7.0 mmol) and propylamine-^{15}N hydrochloride (0.96 g, 10.0 mmol) in water (50 mL) was added sodium hydroxide (0.4 g, 10.0 mmol) in water (25 mL) dropwise with stirring, and the reaction mixture was refluxed for 10 h, until the evolution of H$_2$S ceased. The solvent was removed under reduced pressure. The solid residue was extracted with CHCl$_3$ (3 × 50 mL) and dried (Na$_2$SO$_4$), and the solvent was removed to afford 520 mg (64% yield) of thiourea **15**: mp 65 °C; ^{13}C NMR (CDCl$_3$) δ 11.14 (C$_3$, C$_3$′), 22.39 (C$_2$, C$_2$′), 46.06 (d, $^1J(^{13}C–^{15}N)$ = 10.5 Hz), 180.50 (d, C=S, $^1J(^{13}C–^{15}N)$ = 16.5 Hz); MS, *m/e* (relative intensity) 162.0973 (100.00; calcd for $C_7H_{16}N_2S$, 162.0975); ^{15}N NMR (acetone-d_6) 109.3 ppm.

The above thiourea (400 mmol, 2.5 mmol) was nitrosated with Na^{15}NO$_2$ (350 mg, 5.0 mmol) in the presence of 0.1 N HCl (60 mL), and after the usual workup the nitrosothiourea **3a** was obtained: 350 mg (73%); heavy oil; ^{1}H NMR (acetone-d_6) δ 0.85 (t, 3 H, CH$_3$), 1.00 (t, 3 H, CH$_3$), 1.46 (m, 2 H, CH$_2$), 1.82 (m, 2 H, CH$_2$), 3.85 (m, 2 H, CH$_2$), 4.20 (t, 2 H, CH$_2$), 9.85 (dtdd, 1 H, NH, exch, $^1J(^{15}N_3–H)$ = 92.7 Hz, ^2J(H–H) = 5.5 Hz, $^3J(^{15}N_1–N_3H)$ = 1.8 Hz, $^4J(^{15}NN_2O–N_3H)$ = 1.8 Hz; MS, *m/e* (relative intensity) 192.0847 (17.08, M$^+$; calcd for $C_7H_{15}{}^{15}N_3OS$, 192.0847), 161.0897 (52.47; calcd for $C_7H_{15}{}^{15}N_2S$, 161.0897), 90.0578 (1.20; calcd for $C_3H_8{}^{15}N_2O$, 90.0577), 59.0652 (100.00; calcd for $C_3H_8{}^{15}N_1$, 59.0627).

1,3-Diethyl-1-(nitroso-^{15}N)thiourea-*1,3*-$^{15}N_2$ (2a). A solution of CS$_2$ (280 mg, 5 mmol) and ethylamine-^{15}N hydrochloride (500 mg, 5 mmol) in the presence of sodium hydroxide (150 mL) with the method described for **3a** afforded 1,3-diethylthiourea-*1,3*-$^{15}N_2$ (**14**): 480 mg (72% yield); mp 78 °C; ^{13}C NMR (CDCl$_3$) 14.53 (C$_2$, C$_2$′), 39.20 (d, C$_1$, C$_2$′, $^1J(^{15}N–^{13}C)$ = 10.5), 181.32 (d, C=S $^1J(^{15}N–^{13}C)$ = 16.5 Hz); ^{15}N NMR (acetone-d_6) 109.3 ppm; MS, *m/e* (relative intensity) 134.0662 (100.00, calcd for $C_5H_{12}{}^{15}N_2S$, 134.0662), 73.0554. The above thiourea (**14**) was nitrosated with Na^{15}NO$_2$ in 0.7 N HCl to afford the nitrosothiourea **2a** as a viscous oil: 350 mg (64% yield); MS, *m/e* (relative intensity) 164.0537 (19.82, M$^+$; calcd for $C_5H_{11}{}^{15}N_3OS$, 164.0534), 133.0587 (100.00; calcd for $C_5H_{11}{}^{15}N_2S$, 133.0583), 76.0423 (5.96; calcd for $C_2H_6{}^{15}N_2O$, 76.0421).

3-Cyclohexyl-1-ethyl-1-(nitroso-^{15}N)thiourea-*3*-^{15}N (7a). A solution of ethyl isothiocyanate (700 mg, 8 mmol) and cyclohexylamine-^{15}N (800 mg, 8 mmol) in ether (100 mL) was stirred for 12 h at ambient temperature and after the usual workup gave the thiourea **17**: 1.10 g (73% yield); ^{1}H NMR (acetone-d_6) δ 1.15 (t, 2 H, CH$_3$), 1.20–2.20 (m, 10 H, CH$_2$), 3.52 (m, 2 H, CH$_2$), 4.20 (br m, 1 H, H$_1$′ axial), 6.85 (dd, 1 H, NH, exch, $^1J(^{15}N–H)$ = 90.0 Hz, ^2J(H–H) = 8.0 Hz); MS, *m/e* (relative intensity) 187.1161 (100.00; calcd for $C_9H_{18}H^{15}NS$, 187.1161), 99.0939 (48.81; calcd for $C_6H_{12}{}^{15}N$, 99.0857). The above thiourea (1.0 g, 5.3 mmol) was nitrosated with Na^{15}NO$_2$ (420 mg, 6.0 mmol) in the usual manner to afford 600 mg (63%) of nitrosothiourea **7a**: ^{1}H NMR (acetone-d_6) δ 1.00 (t, 2 H, CH$_3$), 1.10–2.20 (m, 10 H, CH$_2$), 4.20 (q, 2 H, CH$_2$), 4.40 (m, 1 H, H$_1$′, axial), 9.30 (ddd, 1 H, NH, exch, $^1J(^{15}N–H)$ = 91.0 Hz, ^2J(H–H) = 8.0 Hz, $^3J(^{15}N=O)$ = 8.0 Hz); MS, *m/e* (relative intensity) 187.1161 (100.00; calcd for $C_9H_{18}N^{15}NS$, 187.1161), 99.0939 (48.81; calcd for $C_6H_{12}{}^{15}N$, 99.0857), 186.1085 (78.95, M$^+$ − ^{15}NO; calcd for $C_9H_{17}N^{15}NS$, 186.1084), 152.1201 (3.12; calcd for $C_9H_{15}N^{15}N$, 152.1201), 99.0941 (100.00; calcd for $C_6H_{12}{}^{15}N$, 99.0941); ^{13}C NMR (acetone-d_6) 12.24 (C$_2$), 25.73 (C$_3$′, C$_5$′), 26.11 (C$_4$′), 31.88 (C$_2$′, C$_6$′), 39.22 (C$_1$), 55.95 (C$_1$′, $J(^{15}N–^{13}C)$ = 10.5), 178.70 ($^1J(^{15}N–^{13}C)$ = 18.4, $^2J(^{15}N–^{13}C)$ = 4.1 Hz).

1,3-Dimethyl-1-(nitroso-^{15}N)thiourea-^{13}C (18). This compound was prepared as described previously.[1]

1,3-Diethyl-1-(nitroso-^{15}N)thiourea-^{13}C (19). The 1,3-diethylthiourea was obtained (710 mg, 82% yield) from CS$_2$ (0.5 g, 90% ^{13}C enriched, 6.5 mmol) and ethylamine (900 mg, 10.0 mmol) in water with stirring for 2 h at room temperature, refluxing for 12 h, and the usual workup: MS, *m/e* (relative intensity) 133.0756 (100.00; calcd for $C_4{}^{13}C_1H_{12}N_2S$, 133.0755), 72.0648 (12.72; calcd for $C_2{}^{13}C_1H_7N_2$, 72.0643).

The above thiourea (660 mg, 5 mmol) was nitrosated with Na^{15}NO$_2$ (420 mg, 6 mmol) in the usual manner to afford 550 mg

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(65%) of 1,3-diethyl-1-(nitroso-^{15}N)-thiourea-^{13}C (**19**): MS, *m/e* (relative intensity) 163.0626 (52.32; calcd for $C_4{}^{13}C_1H_{11}N_2{}^{15}N_1OS$, 163.0626); 132.0676 (100.00; calcd for $C_4{}^{13}C_1H_{11}N_2S$, 132.0676), 88.0181 (18.98; calcd for $C_2{}^{13}C_1H_5NS$, 88.0176).

1,3-Dipropyl-1-(nitroso-^{15}N)thiourea-^{13}C (20). A solution of $^{13}CS_2$ (0.5 g, 90% ^{13}C, 6.5 mmol) and propylamine (0.7 g, 10.2 mmol) in water (100 mL) was stirred for 2 h at room temperature and refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was triturated with petroleum ether to afford 1,3-dipropylthiourea-^{13}C: 810 mg (82%); ^{13}C NMR (acetone-d_6) δ 11.62 (C_3, C_3'), 23.16 (C_2, C_2'), 46.46 (C_1, C_1'), 184.15 (C=S); MS, *m/e* (relative intensity) 161.1068 (77.85; calcd for $C_6{}^{13}C_1H_{16}N_2S$, 161.1068), 58.0682 (100.00; calcd for C_3H_8N, 58.0657).

The above thiourea (800 mg, 50 mmol) was nitrosated with $Na^{15}NO_2$ (0.4 g, 5.7 mmol) and 50 mL (0.1 N HCl) at -10 °C, and after the usual workup it afforded *N*-nitrosothiourea **20**: 650 g (68% yield); an oil; MS, *m/e* (relative intensity) 191.0938 (21.36; calcd for $C_6{}^{13}C_1H_{15}N_2{}^{15}N_1OS$, 191.0940); 160.0989 (46.58; calcd for $C_6{}^{13}C_1H_{15}N_2S$, 160.0989), 58.0682 (100.00; calcd for C_3H_8N, 58.0657).

3-Cyclohexyl-1-ethyl-1-(nitroso-^{15}N)thiourea-^{13}C (21). To a solution of cyclohexylamine (680 mg, 6.8 mmol) and excess of triethylamine (2 mL) in water (25 mL) was added slowly a solution of 1,3-diethyl-1-nitrosothiourea-^{13}C (1.10 g, 6.8 mmol) in ether (10 mL), and the reaction mixture was stirred at ambient temperature for 12 h. The solid which separated was collected and washed with petroleum ether to afford the 3-cyclohexyl-1-ethylthiourea-^{13}C: 1.0 g (79% yield); ^{13}C NMR ($CDCl_3$) 14.29 (C_2), 24.77 (C_3', C_5') 25.45 (C_4'), 33.04 (C_2', C_6'), 39.00 (C_1), 53.12 (C_1'), 180.39 (C=S); MS, *m/e* (relative intensity) 187.1218 (100.00; calcd for $C_8{}^{13}C_1H_8N_2S$, 187.1225), 89.0254 (15.24; calcd for $C_2{}^{13}C_1H_6NS$, 89.0254).

The above thiourea (930 mg, 50 mmol) was nitrosated with $Na^{15}NO_2$ (500 mg, 7.1 mmol) by the usual procedure to afford 630 mg (56% yield) of 3-cyclohexyl-1-ethyl-1-(nitroso-^{15}N)thiourea-^{13}C (**6a**): ^{13}C NMR (acetone-d_6) δ 12.24 (C_2'), 25.74 (C_3, H_5'), 26.24 (C_4'), 31.36 (C_3', C_5'), 39.60 (C_1'), 56.07 (C_1), 178.50 $^2J(^{15}N-^{13}C)$ = 3.7 Hz); MS, *m/e* (relative intensity) 217.1095 (1.49; calcd for $C_8{}^{13}C_1H_{17}N_2{}^{15}N_1OS$, 217.1095), 186.1146 (50.07; calcd for $C_8{}^{13}C_1H_{17}N_2S$, 186.1146), 98.0966 (100.00; calcd for $C_8H_{12}N$, 98.0970).

Note: All *N*-nitrosothioureas should be handled with extreme care owing to the potential mutagenicity.

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Registry No. **1**, 79645-01-5; **2**, 79645-03-7; **2a**, 84051-04-7; **3**, 84050-92-0; **3a**, 84051-01-4; **4**, 84050-93-1; **5**, 84050-94-2; **6**, 79645-02-6; **6a**, 84051-12-7; **7**, 79645-04-8; **7a**, 84051-06-9; **8**, 84050-95-3; **9**, 84050-96-4; **10**, 79645-05-9; **11**, 84056-92-8; **12**, 3715-92-2; **12a**, 84051-13-8; **13**, 24790-99-6; **14**, 84051-03-6; **15**, 84051-00-3; **17**, 84051-05-8; **19**, 84051-08-1; **20**, 84051-09-2; CS_2, 75-15-0; $^{13}CS_2$, 30860-31-2; imidazolinidine-2-thione, 872-35-5; 1-(2-hydroxyethyl)imidazolidine-2-thione, 932-49-0; imidazolidine-2-thione-1,3-$^{15}N_2$, 84050-97-5; 1,2-diaminoethane-$^{15}N_2$ dihydrochloride, 84050-98-6; pripylamine-^{15}N hydrochloride, 84050-99-7; ethylamine-^{15}N hydrochloride, 84051-02-5; ethylisothiocyanate, 542-85-8; cyclohexylamine-^{15}N, 78441-12-0; 1,3-diethyl-1-thiourea-^{13}C, 84051-07-0; 1,3-dipropyl-1-thiourea-^{13}C, 84051-10-5; cyclohexylamine, 108-91-8; 3-cyclohexyl-1-ethylthiourea-^{13}C, 84051-11-6; propylamine, 107-10-8.

Stereochemistry and Regiochemistry of Electron Impact, Thermally and Photolytically Induced Eliminations from 1-Decalyl Acetates

G. Eadon,* C. Alonso, and H. Valente

Department of Chemistry, State University of New York at Albany, Albany, New York 12222

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Deuterium labeled compounds are used to define the stereochemistry and regiochemistry of the electron impact induced elimination of acetic acid from *trans,trans*-1-decalyl acetate and *trans,cis*-1-decalyl acetate. Both compounds fragment with very predominant equatorial (2α) hydrogen abstraction. Since the trans equatorial hydrogen of the *trans,trans*-acetate **3** cannot be approached within the requisite 1.8 Å by the acetate carbonyl in any boatlike conformer, this result demonstrates that hydrogen abstraction largely occurs from the chair conformer of the intact cyclohexyl ring. The regiochemistry of the Norrish type II photolysis of the corresponding phenylacetate **5** is also consistent with predominant C-2α hydrogen abstraction, while the pyrolysis of the acetate **3** exhibits different regiochemistry. The similarity between mass spectral and photolytic behavior and the difference between mass spectral and pyrolytic behavior suggest that the mass spectral process is nonconcerted. Although the tertiary C-8 hydrogen has a greater intrinsic migratory aptitude than the secondary C-2 hydrogens, stereochemical effects clearly are predominant in the mass spectral behavior of these acetates.

The well-known bond lengths and angles of the chair conformer of the cyclohexyl ring have been exploited to elucidate the stereochemistries and mechanisms of many reactions. Mass spectroscopists have generally not attempted analogous studies on electron impact induced fragmentations because many of these reactions apparently occur through highly excited, conformationally ill-defined, boatlike conformers. For instance, the dehydration of cyclohexanols by electron impact is a 1,4-elimination through such boatlike conformers.[1] The elimination of acetic acid from 1-tetralyl acetate has also been found to involve almost exclusive 1,4-elimination via a boatlike conformer.[2] In contrast, however, evidence has been advanced that *cis*- and *trans*-4-alkylcyclohexyl acetates, several related cyclohexyl derivatives, and *trans,trans*- and *trans,cis*-2-decalyl acetates undergo γ-hydrogen abstraction predominantly while in the stable chair conformation.[3-7] A major piece of evidence on behalf of this hy-

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